AMENDMENTS TO THE SPECIFICATION:

Please delete the paragraph submitted in the Preliminary Amendment filed May 27, 2004, which is labeled "Cross-Reference to Related Applications"

Please replace paragraph [0010] with the following:

[0010] HIF1α plays an important role in promoting tumor progression and is overexpressed in common human cancers, including breast, colon, lung, and prostate carcinoma. Overexpression of HIFs is sometimes observed in cancers, such as clear [[cel]] cell renal cell carcinoma, even at normoxia. Mutations that inactivate tumor suppressor genes or activate oncogenes have, as one of their consequences, upregulation of HIF1α activity, either through an increase in HIF1α protein expression, HIF1α transcriptional activity, or both (Semenza, *Pediatr. Res.*, **2001**, *49*, 614-617).

Please replace paragraph [0019] with the following:

[0019] Preeclampsia is a disorder of unknown etiology that is the leading cause of fetal and maternal morbidity and mortality. Defective downregulation of HIF1α may play a major role in the pathogenesis of preeclampsia. For most of the first trimester, the human fetus develops under hypoxic conditions but at 10-12 weeks the intervillous space opens, the fetus is exposed to maternal blood and at this stage the trophoblast cells invade the maternal decidua. The switch of the trophoblasts from a proliferative to an invasive phenotype is controlled by cellular oxygen concentration. The proliferative, non-invasive trophoblast phenotype appears to be maintained by HIF1α mediated expression of TGFbeta3 because treatment of human villous explants with an antisense oligonucleotide against HIF1α or TGF beta 3 induces invasion under hypoxic conditions. In this case the HIF1α antisense ~~oligonucelotide~~ oligonucleotide was comprised of phosphorothioate oligonucleotides, 16 nucleotides in length, and targeted to the AUG codon (Caniggia *et al., J. Clin. Invest.*, **2000**, *105*, 577-587.; Caniggia *et al., Placenta*, **2000**, *21 Suppl A*, S25-30).

Please replace paragraph [0025] with the following:

[0025] HIF2α mRNA is primarily expressed in highly vascularized adult tissues, such as lung, heart and liver, and in the placenta and endothelial cells of the embryonic and adult mouse (Hogenesch *et al., J. Biol. Chem.*, **1997**, *272*, 8581-8593). Comparison of normal human

tissues and cancers reveals that HIF2α protein is not detectable in normal tissue, but is easily visualized in malignant tissues (Talks *et al.*, *Am. J. Pathol.*, **2000**, *157*, 411-421). The requirement for expression of HIF2α in development is demonstrated by the abnormalities observed in HIF2α gene deficient mouse ~~embyros~~ embryos, which include the disruption of catecholamine homeostasis and lack of protection against heart failure observed (Tian *et al.*, *Genes Dev.*, **1998**, *12*, 3320-3324). Targeted disruption of the HIF2α gene and generation of embryos deficient for HIF2α is disclosed in the PCT publication WO 02/086497 (Compernolle *et al.*, **2002**). This publication also discloses antisense oligodeoxyribonucleotides for use in inhibiting HIF2α expression targeted to the translation initiation codon of HIF2α (Compernolle *et al.*, 2002).

Please replace paragraph [0031] with the following:

[0031] A link between elevated HIF2α activity and angiogenesis has also been demonstrated by experiments that show how HIF activity regulates VEGF expression. Normal human kidney cells typically have low levels of hypoxia-inducible factor 2 alpha, but upon introduction of a vector encoding HIF2α into these cells, VEGF mRNA and protein levels increase significantly (Xia *et al.*, *Cancer*, **2001**, *91*, 1429-1436). When HIF2α was inhibited, VEGF expression was significantly decreased, thus demonstrating a direct link between HIF2α activity and VEGF expression (Xia *et al.*, *Cancer*, **2001**, *91*, 1429-1436). Similarly, a dose-dependent increase in VEGF mRNA is observed when human ~~umbulical~~ umbilical vein cells are transduced with a virus encoding HIF2α (Maemura *et al.*, *J. Biol. Chem.*, **1999**, *274*, 31565-31570). Expression of a mutated HIF2α that lacks a transactivation domain inhibits the induction of VEGF mRNA during hypoxia, a finding that further suggests that HIF2α is an important regulator of VEGF expression (Maemura *et al.*, *J. Biol. Chem.*, **1999**, *274*, 31565-31570).

Please replace paragraph [0035] with the following:

[0035] Short interfering RNAs (siRNAs) have been used to specifically inhibit the expression of HIF1α and HIF2α in human breast and renal carcinoma cell lines and in a human endothelial cell line. SiRNA duplexes with dTdT overhangs at both ends were designed to target nucleotides 1521-1541 and 1510-1530 of the HIF1α mRNA ~~squence~~ sequence (NM001530) and nucleotides 1260-1280 and 328-348 of the HIF2α sequence (NM001430). It was found that in the breast carcinoma and endothelial cell lines, gene expression and cell migration patterns were

critically dependent on HIF1α but not hypoxia-inducible factor-2 alpha, but critically dependent on HIF2α in the renal carcinoma cells. Sowter *et al.*, **2003**, *Cancer Res., 63*, 6130-6134.

Please replace paragraph [0050] with the following:

[0050] The present invention provides compositions and methods for modulating HIF1α and HIF2α expression. In particular antisense compositions for modulating HIF1α and/or HIF2α expression are believed to be useful in treatment of abnormal proliferative conditions associated with HIF1α and/or HIF2α. Examples of abnormal proliferative conditions are hyperproliferative disorders such as cancers, tumors, hyperplasias, pulmonary fibrosis, angiogenesis, psoriasis, atherosclerosis and smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following ~~antioplasty~~ angioplasty. It is presently believed that inhibition of both HIF1α and HIF2α may be a particularly useful approach to treatment of such disorders.

Please replace paragraph [0089] with the following:

[0089] Such double stranded oligonucleotide moieties have been shown in the art to modulate target expression and regulate translation as well as RNA ~~processing~~ processing via an antisense mechanism. Moreover, the double-stranded moieties may be subject to chemical modifications (Fire *et al.*, *Nature*, **1998**, *391*, 806-811; Timmons and Fire, *Nature* **1998**, *395*, 854; Timmons *et al.*, *Gene*, **2001**, *263*, 103-112; Tabara *et al.*, *Science*, **1998**, 282, 430-431; Montgomery *et al.*, *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 15502-15507; Tuschl *et al.*, *Genes Dev.*, **1999**, *13*, 3191-3197; Elbashir *et al.*, *Nature*, **2001**, *411*, 494-498; Elbashir *et al.*, *Genes Dev.* **2001**, *15*, 188-200). For example, such double-stranded moieties have been shown to inhibit the target by the classical hybridization of antisense strand of the duplex to the target, thereby triggering enzymatic degradation of the target (Tijsterman *et al.*, *Science*, **2002**, *295*, 694-697).

Please replace paragraph [0168] with the following:

[0168] RNA strands of the duplex can be synthesized by methods disclosed herein or purchased from Dharmacon Research Inc., (Lafayette, CO). Once synthesized, the complementary strands are annealed. The single strands are ~~aliquoted~~ aliquotted and diluted to a concentration of 50 uM. Once diluted, 30 uL of each strand is combined with 15uL of a 5X solution of annealing buffer. The final concentration of said buffer is 100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, and 2mM magnesium acetate. The final volume is 75 uL. This

solution is incubated for 1 minute at 90°C and then centrifuged for 15 seconds. The tube is allowed to sit for 1 hour at 37°C at which time the dsRNA duplexes are used in experimentation. The final concentration of the dsRNA duplex is 20 uM. This solution can be stored frozen (-20°C) and freeze-thawed up to 5 times.

Please replace paragraph [0181] with the following:

[0181] The mouse brain endothelial cell line b.END was obtained from Dr. Werner Risau at the Max Plank ~~Instititute~~ Institute (Bad Nauheim, Germany). b.END cells were routinely cultured in DMEM, high glucose (Gibco/Life Technologies, Gaithersburg, MD) supplemented with 10% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 96-well plates (Falcon-Primaria #3872) at a density of 3000 cells/well for use in RT-PCR analysis.

Please replace paragraph [0191] with the following:

[0191] Analysis of the ~~genootype~~ genotype of the cell (measurement of the expression of one or more of the genes of the cell) after treatment is also used as an indicator of the efficacy or potency of the HIF1α and/or HIF2α inhibitors. Hallmark genes, or those genes suspected to be associated with a specific disease state, condition, or phenotype, are measured in both treated and untreated cells.